E27

Hoechst

Final

EFFICACY REPORT

08 January 1997

based on the survey

A double-blind placebo-controlled four-way parallel group trial to evaluate the efficacy of Octopirox 0.75% compared to Zinc pyrithione 1% and Climbazole 0.75% in the treatment of seborrhoeic dandruff of the scalp

Hoechst Trial No. HAG 158 95
PAREXEL Project No. 7 / 7993

Clinical Trial Director	Prof. Dr. Merani Thianprasit
Survey dates	31 Oct. 1995 - 07 Apr. 1996 enrollment and treatment phase

SIGNATURES

The undersigned confirm that this report appropriately reflects the efficacy findings and conclusions of this survey.

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1. INTRODUCTION

Seborrhoeic dandruff is a common skin disease affecting about 1-3% of the population. Its clinical symptoms are characterised by erythematous scaly lesions of the scalp, face and trunk. The pathogenetic mechanism of the disease includes infection with fungal organisms (Shuster 1984), with the yeast *Pityrosporum ovale* having been described as an important pathogen since the last century (e.g. Rivolta 1873). This mechanism enabled the development of antifungal therapy as an effective treatment (Farr & Shuster 1984; Ford et al. 1984).

Since the late seventies, Octopirox has been well established as an active ingredient in shampoos for the treatment of seborrhoeic dandruff (Hewin 1994).

The present survey was primarily intended to assess the efficacy of Octopirox shampoo in the treatment of seborrhoeic dandruff of the scalp in Asian people under tropical conditions compared to vehicle and to two active comparators (Zinc pyrithione and Climbazole).

Octopirox (1-Hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2(1H)-pyridone, combination with 2-aminoethanol (1:1); Piroctone Olamine) is an antifungal and antibacterial drug of the pyridone class with fungicidal properties against all relevant pathogenic dermatophytes, yeasts and molds. Like other pyridones, it exerts its antifungal efficacy by inhibiting cellular uptake of essential substances into fungal cells. Moreover, by complexing metal ions (especially Fe^{3+}), pyridones inhibit the energy metabolism in the fungal mitochondria. Apart from the antifungal properties, Octopirox shows bactericidal activity against both, gram-positive and gram-negative organisms.

Zinc pyrithione is a chelated complex of zinc with 2-pyridinethiol-1-oxide, also known as Bis [1 - hydroxy - 2(1H)- pyridinethionato - O,S] - (T-4) zinc. It has been found effective against gram-positive and gram-negative bacteria, fungi, yeasts and molds. Zinc pyrithione is a complex of zinc with two molecules of the parent compound, N-hydroxy-2-pyridinethione.

Climbazole, also known as 1-(4-Chlorophenoxy)-1-(1H-Imidazolyl)-3,3-Dimethyl-2-Butanone, is an antimycotic agent belonging to the class of Imidazole-derivatives. It shows activity against molds, yeasts and dermatomyces and against gram-positive and gram-negative organisms.

The present report briefly explains the survey conduct and summarises the most important findings. This includes also additional analyses not given in the full report of the survey, which was prepared separately (PAREXEL No. 50/2363-95) as scheduled in the protocol.

2. SURVEY OBJECTIVE

The objective of the present survey was to assess under tropical conditions the efficacy of Octopirox shampoo 0.75 % compared to Zinc pyrithione 1 %, Climbazole 0.75 % and vehicle in the treatment of seborrhoeic dandruff of the scalp in Asian people.

3. INVESTIGATIONAL PLAN

The survey was conducted in Thailand according to protocol HAG 158 95 (dated 18 October 1995) under the scientific supervision of the Trial Director Prof. Dr. Merani Thianprasit, Bangkok. There was one protocol amendment (dated 5 December 1995) which stated that 'Subjects will be allowed to perform multiple shampooing of the hair upon each hair washing'. This modification reflects the common local habits for hair care.

Design

The survey consisted of a 3-week vehicle run-in phase, a 5-week treatment period and a 2-week follow-up period. The duration for each subject participation was to be 10 weeks (70 days) as shown below.

	3 weeks **Vehicle-run-in**		5 weeks **Experimental**		2 weeks **Follow-up**
Visit	**1** *Screening*	**2** *Randomisation*	**3** *Interim visit*	**4** *Final assessment*	**5**
Treatment	Shampoo vehicle		Active shampoo		Shampoo vehicle

During the 3-week vehicle-run-in period all subjects were treated with the pure shampoo base, which has no antifungal activity. On completion of the run-in period, the subjects were finally enrolled into the experimental part of the survey on the basis of an evaluation during the baseline visit (visit 2).

The experimental period of the survey was performed using a randomised, double blind, parallel design. During the baseline visit all eligible subjects were randomised into four parallel groups with twice weekly applications of either of four different

treatment regimens as specified below. After an interim visit two weeks following the start of randomised treatment (visit 3), the final efficacy assessment were performed at visit no. 4 (after 5 weeks of active treatment).

After the experimental survey phase, all subjects were to enter a 2-week follow-up period for monitoring possible recurrences. During this follow-up period, the subjects had to apply the non-antifungal shampoo base and were to be assessed clinically at visit no. 5 (after 2 weeks of shampoo base) for symptoms of possible recurrences.

The efficacy variables assessed at each of the 5 survey visits were ordinal scales for scaling, itching and inflammation as well as the assessment of the percentage of affected scalp area and an additional description (absence or presence of moistening, pustules, scratch marks).

The survey was carried out in 17 centers with a total of 288 enrolled subjects. The overall duration of the survey was about seven months.

All centers were either hospitals or central health centers; all investigators were dermatologists. Prior to survey onset an investigator meeting took place in order to ensure standardised application of all methods and procedures.

Survey medication and dosage

The following four test shampoos were used for the survey:

INN	**Piroctone Olamine**	**Zinc pyrithione**	**Climbazole**	**Vehicle**
Trade name	OCTOPIROX	ZINC OMADINE	BAYPIVAL	
CAS No.	68890-66-4	13463-41-7	38083-17-9	
Batch	HU303 (Labor Nr.)	HU305 (Labor Nr.)	HU304 (Labor Nr.)	
Concentration	0.75 %	1.0 %	0.75 %	-
Dosage form	Shampoo			
Single dose	5 ml			
Frequency	twice weekly (1 to 3 doses per application, depending on hair length)			
Date of manufacture	15. Sept.1995 (for all substances)			

The shampoo base was identical for all treatments. It contained sodium ether sulfate and alkylamidopropylbetaine (Na-LES + CAPB, 8:2). The total detergent concentration was 15 % (AI = 15 %).

The application volume of the test shampoos depended on the hair length:

hair length	short:	1 x 5 ml
	medium:	2 x 5 ml
	long:	3 x 5 ml

Treatments were to be applied as outlined in the overall treatment schedule below:

Survey period	3 weeks **Vehicle-run-in**		5 weeks **Experimental**		2 weeks **Follow-up**
Visit	**1** *Screening*	**2** *Randomisation*	**3** *Interim visit*	**4** *Final assessment*	**5**
Group 1	Shampoo		vehicle, twice weekly		Shampoo
Group 2	vehicle		Octopirox 0.75 %, twice weekly		vehicle
Group 3	up to		Zinc pyrithione 1.0%, twice weekly		up to
Group 4	once daily		Climbazole 0.75 %, twice weekly		once daily

The investigator dispensed the relevant shampoo to be tested only to subjects who had been included in the survey following the procedures set out in the protocol. At visits 1 and 2 (see table below) the subjects were provided with a 500 ml plastic bottle containing the individual shampoo supply for the relevant time period. In addition, at visit 2 the subjects received a notebook for the documentation (date/time) of each single application of the randomised shampoo and an alarm clock to help ensure that the application time was adhered to.

Run-in phase

During the 3-week vehicle run-in period all subjects with short hair were required to apply 1 x 5 ml shampoo base (for subjects with hair of medium length 2 x 5 ml, for subjects with long hair 3 x 5 ml) up to once daily.

During run-in, no other cosmetic or non-cosmetic treatment of the scalp or the hair except that provided for the survey was allowed, with the exception of hair-spray, hair setting lotion, hair-tinting lotion.

Experimental survey period

For the 5-week experimental survey period , the subjects were randomised into four parallel groups with different shampoos.

Each randomised shampoo application was to be performed according to the following sequence:

1. wetting the hair,
2. lathering and thorough massage with the entire amount of shampoo provided for one application,
3. incubation time of 3 min., controlled by an alarm clock
4. dispensed to each subject,
5. rinsing of the hair.

The time interval between consecutive applications of the test shampoo was to be about three days. During the interval between the applications of the test shampoo the additional use of the shampoo base was allowed. The time interval between a visit to the test unit and the preceding application of the test shampoo was to be at least 2 days. Deviations of ± 3 days with reference to the required visiting schedule was accepted.

Follow-up period

During the 2-week follow-up phase all subjects were allowed to use the shampoo base daily. No other cosmetic or non-cosmetic treatment of the scalp or the hair except that provided for the survey was allowed, with the exception of hair-spray, hair setting lotion, hair-tinting lotion.

Survey population

Selection

Inclusion criteria

The following criteria were to be met to allow enrollment of a subject in the survey:

- age >18,
- good physical health (according to a brief medical history and physical examination),
- diagnosis of stable or exacerbating seborrhoeic dandruff of the scalp as evidenced by:
  -- scaling score 2 to 4,
  -- inflammation score 2 to 4 (see below for description of scores),
- written or verbal informed consent.

Exclusion criteria

Subjects meeting any of the following exclusion criteria were not be included in the survey:

- mental condition rendering the subject unable to understand the nature, scope and possible consequences of the survey
- history or a suspicion of unreliability, poor co-operation or non-compliance with the treatment,
- psoriasis,
- atopic dermatitis,
- topic treatment of the scalp with any other antifungal preparation or with a corticosteroid in the previous 2 weeks before the start of the run-in phase,
- systemic use of retinoids, erythromycin, tetracycline or any of its deviates (e.g. minocycline hydrochloride, doxycycline), trimethoprim/ sulfamethoxazole, or metronidazole within 28 days before the start of the run-in phase,
- likelihood of requiring treatment during the trial period with drugs not permitted by the survey protocol (see "Concomitant treatment" below),
- history of hypersensitivity to the survey medication or to substances with similar chemical structures,
- severe disease, likely to jeopardise the planned termination of the survey (e.g. cancer, cardiac infarct, instable angina pectoris).

Under no circumstances were subjects be enrolled into this survey more than once. Subjects who left the survey prematurely after randomisation were not replaced.

Sample size

The planned sample size was chosen according to commonly applied statistical considerations.

The main focus was on the comparison of Octopirox vs. vehicle, which was performed using the Wilcoxon rank-sum test adjusted for centres (Cochran-Mantel-Haenszel test with modified ridit scores; Lehman 1975). Assuming 50 evaluable subjects per group, a t-test would detect a mean difference of 0.57 x SD (0.65 x SD) between Octopirox vehicle (2-sided, alpha-level = 5%) with a power of 80% (90%). Since the Wilcoxon rank-sum test is less powerful, compared to the t-test, the anticipated sample size of approximately 55 subjects per group for the intent-to-treat analysis appears to be adequate.

It was intended to include a total of 280 subjects; an actual total of 288 subjects was enrolled. See the results section for the disposition of the subjects across the different treatment groups.

Randomisation

The randomisation was performed by PAREXEL in blocks. Subjects received their randomisation number consecutively in the order in which they entered the experimental survey phase. Complete blocks of subject numbers were assigned to each survey centre. The number of subjects per centre was planned to be 8 to 16. The test substances were allocated randomly to the subject numbers in advance, by PAREXEL. Each subject was to be given only the test substances carrying his/her individual number.

Variables and schedule of observations

Efficacy variables

The efficacy was assessed using the following variables:

A. ordinal Scaling score	0	none	
	1	slight	small flakes resembling a coarse greyish powder
	2	mild	intermediate
	3	moderate	large flakes very loosely attached to the scalp and given an irregular whitish surface
	4	pronounced	flakes apparently congealed together into yellowish plates adhering to the scalp
	5	severe	asbestos-like scaling.

B. Proportion of scalp area affected

The percentage of the scalp surface affected by the disease was estimated as follows:

0	0 - 10 %
1	>10 - 20 %
2	>20 - 30 %
3	>30 - 50 %
4	>50 - 75 %
5	>75 - 100 %

The variables A and B were combined, thus forming a sumscore (sumscore 2) ranging from 0 to 10. This sumscore 2 was scheduled during the course of analysis.

Further efficacy parameters were

C. ordinal Itching score	0	none
	1	slight
	2	mild
	3	moderate
	4	pronounced
	5	severe

D. ordinal Inflammation score (Erythema)

0 none
1 slight
2 mild
3 moderate
4 pronounced
5 severe

E. Additional description

The following items of the disease were scored as absent or present

- moistening
- pustules
- scratch marks

The itching score was self-assessed by each subject. All other assessments were carried out by the investigator. For statistical evaluation the results of three single scores A, C and D were added, thus forming the combined score from 0 to 15 (sumscore 1).

Clinical variables

At screening a physical examination was performed with regard to the in- and exclusion criteria.

Concomitant illness and medication

All treatments taken by the subjects on entry in the survey and all treatments given in addition to the survey treatment were regarded as concomitant treatments and were documented on the case record form.

The following concomitant treatments were NOT permitted during the survey, either given topically (i.e. when used in the region of the scalp) or systemically (see also exclusion criteria):

- any cosmetic or non cosmetic treatment of the scalp or the hair except the survey treatment, hair-spray, hair setting lotion and hair-tinting lotion,
- antimycotics,
- corticosteroids,
- retinoids,
- antibiotics.

Compliance

Compliance was assessed as follows:

Subjects were instructed to return their used bottles with test shampoo to the investigator at visit 4 and the notebooks at visit 3 and 4. Compliance was assessed by weighing the returned bottles (not in the presence of the subject) and by checking their notebooks.

Schedule of observations

The schedule of survey procedures is summarised below.

Survey schedule					
	Vehicle Run-in		Experimental		
	Screening	Baseline			Follow-up
Visit No. (Survey day)	**1** (0)	**2** (21)	**3** (35)	**4** (56)	**5** (70)
Written or verbal agreement	x				
Medical history	x				
Physical examination	x				
Distribution of notebook and alarm clock		x			
Inclusion/exclusion criteria	x	x			
Randomisation		x			
Scaling score	x	x	x	x	x
Area affected	x	x	x	x	x
Itching score	x	x	x	x	x
Inflammation score	x	x	x	x	x
Additional description	x	x	x	x	x
Dispensing of shampoo bottle	x	x			
Test shampoo bottle count/weighing				x	
Notebook check			x	x	
Concomitant treatment recording	x	x	x	x	x

4. STATISTICAL METHODS

The findings were evaluated by the statistical department of PAREXEL. Prior to unblinding the random code, a detailed statistical analysis plan has been generated. The allocation of subjects to the different populations, and - unless otherwise stated - all statistical analyses described below were planned and specified before breaking the code.

Population analysed

For statistical analysis the following populations were predefined.

Screening population	all subjects enrolled
Randomised population	all subjects randomised
Intent-to-treat population (ITT)	all subjects randomised to treatment who received at least one dose of randomised treatment and had a subsequent rating of the sumscore 1
Valid case population (VC)	all ITT subjects who also have a rating of the sumscore 1 at the end of the experimental survey phase (visit 4) and for whom no major protocol violations occurred.

It was planned that if the number of compliant subjects, who complete the five weeks of treatment per protocol, differed substantially from that of the intent-to-treat population (less than 95% of the intent-to-treat population), supplementary descriptive analyses were performed based on these "valid cases" as presented for the sumscore.

Evaluation of the efficacy variable

The primary statistical analysis was performed on an ITT level.

The primary efficacy variable according to protocol was the individual last value during the experimental survey phase of the sumscore derived from the clinical symptoms "scaling", "itching", and "inflammation". The sumscore derived from these clinical symptoms has been summarised by means of descriptive statistics for each visit and at individual endpoint (if appropriate), and for the changes from baseline to each of the measurement points visits.

While the comparison of Octopirox vs. vehicle constitutes the confirmatory part of the analysis according to protocol, the remaining comparisons have to be interpreted at a descriptive level.

Based on the individual endpoint (last value of the sumscore under treatment) pairwise comparisons of the three treatment groups with vehicle have been performed using Wilcoxon rank-sum test adjusted for centers (i.e. the Cochran-Mantel-Haenszel statistic with modified ridit scores).

The variables A - E have been summarised by means of frequency tables (by treatment group and visit) and displayed by bar charts.

Additional analyses and presentation scheduled after unblinding included the depiction of the scaling results using combined scores and the combined presentation of the results for both scaling and area affected (including the sumscore 2).

5. ETHICAL AND LEGAL ASPECTS

Good clinical practice

This survey was carried out in accordance with the provisions of the relevant laws in Thailand and the standard operating procedures for clinical investigation and documentation in force throughout the Hoechst Group worldwide.

Approval of survey protocol

Since this was a survey, it was not necessary to obtain ethics committee approval or comply with any relevant local authorities/legal requirements.

Informed consent of subject

Before treatment, all subjects were informed of the nature, scope and possible consequences of the survey and their informed consent was obtained. Each subjects agreement was confirmed by the signature of the investigator and/or the participating subject The subjects were given an information sheet on the survey.

Confidentiality

The subjects' names and addresses were not made known to the sponsor. Confidentiality was strictly maintained throughout monitoring and auditing of the survey.

6. RESULTS - SURVEY SUBJECTS AND REGIMEN

Disposition of subjects

The subjects' disposition is depicted below.

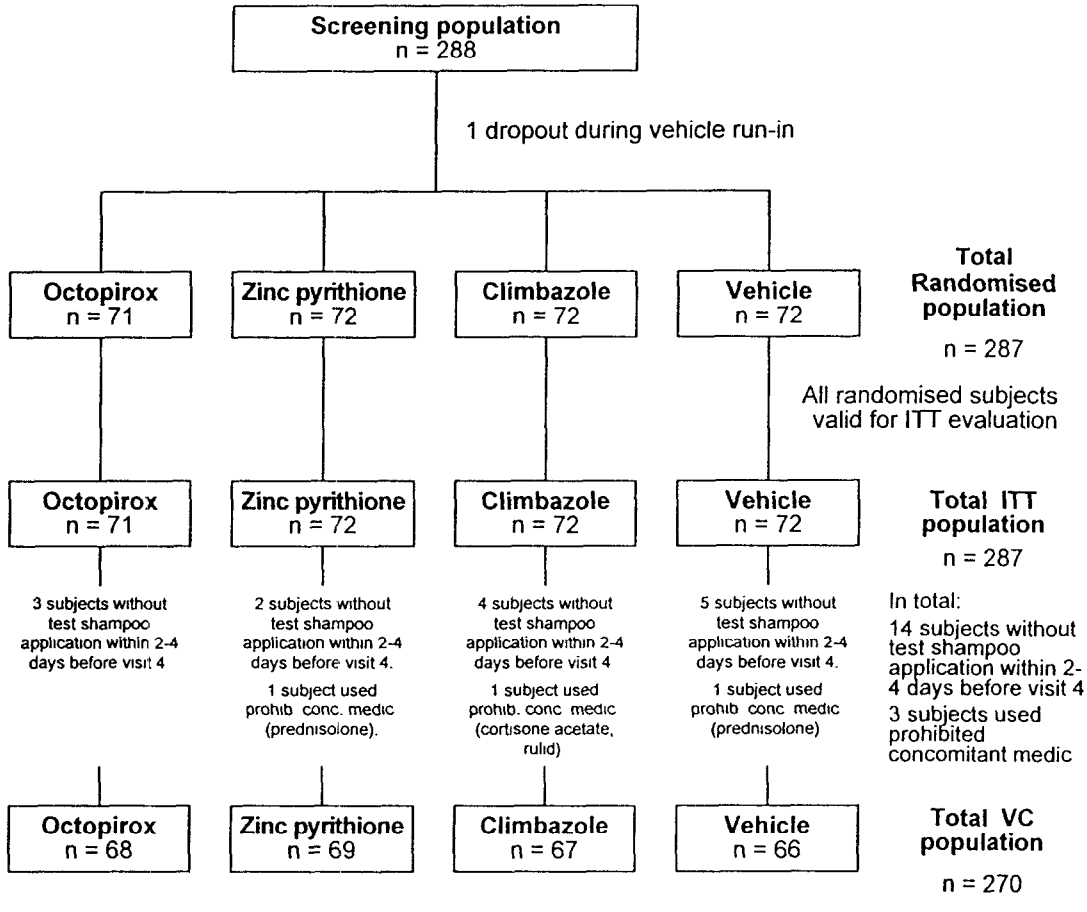


Figure 1
Disposition of subjects

Of the 288 subjects screened (at 17 centres), 287 and 270 were included in the ITT and VC populations, respectively. The sample sizes for the four parallel groups were similar for all analysis populations.

Demographic and background characteristics

Descriptive statistics of the demographic characteristics are provided in Appendix I, Table 3.1. They are summarised below for the ITT population.

Table 1
Demographic data
ITT population (n=287)

	Octopirox 0.75%	Zinc pyrithione 1.0%	Climbazole 0.75%	Vehicle	Total
total n	71	72	72	72	287
males / females	28 / 43	21 / 51	23 / 49	21 / 51	93 / 194
Mean age (a) ± SD	36.3 ± 9.8	34.9 ± 10 6	32.0 ± 9.7	34.3 ± 10.4	34.4 ± 10.2

There was a total of 93 males and 194 females in the ITT population. The predominance of females was seen in all treatment groups. The mean age for males and females was 36.5 and 33.4 years with a range of 17 to 72 years (median 34.0) for the whole population.

Basic illness and previous therapy

Summaries of a known history of allergy, details of existing seborrhoeic dandruff, previous use of vasoactive drugs and any previous treatment (by survey treatment allocation) appear in appendix I, tables 3.2.1., 3.2.2., 3.2.3. and 3.2.4., respectively.

The table below summaries those subjects with a relevant history in the ITT population.

Table 2
Subjects with a relevant history
ITT population (n=287)

History	Number of subjects (%)	
Allergies	23	(8.0%)
Seborrhoeic dandruff	11	(3.8%)
Vasoactive drug use	5	(1.7%)
Previous treatment	42	(14.6%)

Concomitant medication and illnesses

Details of concomitant medications and concomitant diseases for the ITT population appear in tables 3.3.1. and 3.3.2., respectively (Appendix I).

The proportion of subjects with no record of concomitant medication was similar across the treatment groups; it ranged between about 71 % (Zinc pyrithione) and about 78 % (Octopirox). I.e. for most of the subjects, no concomitant medication was recorded.

The most frequently recorded drugs used were chlorpheniramine (n=12) and amoxicillin (n=11).

The most common concomitant diseases in the ITT population were pruritis (n=10), acute upper respiratory infections of unspecified site (n=8) and asthma, unspecified (n=6).

Dosage and duration of treatment

In the four parallel treatment groups, a volume of 1 x 5 ml (short hair), 2 x 5 ml (medium length hair) or 3 x 5 ml (long hair) of 0.0% (vehicle), 0.75% Octopipox, 1.0% Zinc pyrithione and 0.75% Climbazole was applied twice weekly.

Details of the duration of treatment appear in Appendix I, Table 2.4.1. and 2.4.2.

The mean treatment duration was about 32 days; it was very similar in all the treatment groups and both analysis groups.

The compliance was assessed by weighing the bottles with active shampoo that had been returned to the investigator at visit 4 as well as by checking the returned notebooks with information on visit 3 and 4. Information on compliance appear in the list of individual data (section 7) of the full per-protocol survey report (PAREXEL #2363). Compliance was adequate for the purposes of the survey.

7. RESULTS - EFFICACY

Scaling

The percentages of subjects recorded for each assessment category at each survey visit are presented in the table below.

Table 3
Scaling score
Figures denote percentage of subjects ITT population (n=287)

	Octopirox 0.75%					Zinc pyrithione 1.0%					Climbazole 0.75%					Vehicle				
	a	b	c	d	e	a	b	c	d	e	a	b	c	d	e	a	b	c	d	e
V 1	-	-	42.3	45.1	12.7	-	-	48.6	44.4	6.9	-	-	47.2	45.8	6.9	-	-	40.3	56.9	2.8
V 2	-	-	42.3	52.1	5.6	-	-	40.3	52.8	6.9	-	-	43.1	51.4	5.6	-	-	47.2	48.6	4.2
V 3	1.4	49.3	33.8	12.7	2.8	4 2	50.0	27.8	15 3	2 8	1.4	36.1	37.5	23.6	1.4	-	34.7	34.7	29.2	1.4
V 4	9.9	59.2	18.3	11.3	1.4	20.8	50.0	16.7	12.5	-	16.7	51.4	20.8	11.1	-	8.3	44.4	25.0	19.4	2.8
V 5	9.9	46.5	18.3	21.1	4.2	20 8	37.5	23.6	18.1	-	11.1	40.3	34.7	12.5	1.4	9 7	34.7	31.9	20 8	2.8

V 1 = Visit 1 (screening)
V 2 = Visit 2 (baseline)
V 3 = Visit 3
V 4 = Visit 4 (final assessment)
V 5 = Follow up

a = none
b = slight
c = mild
d = moderate
e = pronounced
f = severe (no entry)

As governed by the inclusion criteria, at baseline all subjects presented with a scaling score of "mild" or worse. Hence, the scaling conditions at baseline were well matched across the treatment groups.

For better illustration of the treatment effects, the results for the scaling score after five weeks of treatment are presented below in combined categories.

Table 4
Scaling score after five weeks of treatment - separate and combined categories
Figures denote number and *percentage* of subjects ITT population (n=287)

Scaling score Visit 4:	0 none	1 slight	2 mild	3 moderate	4 pronounced
Octopirox 0.75%	7 *9.9%*	42 *59.2%*	13 *18.3%*	8 *11.3%*	1 *1.4%*
	49 *69.0%*		22 *31.0%*		
Zn-pyrithione 1%	15 *20.8%*	36 *50.0%*	12 *16.7%*	9 *12.5%*	- -
	51 *70.8%*		21 *29.2%*		
Climbazole 0.75%	12 *16.7%*	37 *51.4%*	15 *20.8%*	8 *11.1%*	- -
	49 *68.1%*		23 *31.9%*		
Vehicle	6 *8.3%*	32 *44.4%*	18 *25.0%*	14 *19.4%*	2 *2.8%*
	38 *52.8%*		34 *47.2%*		

Category 5 "severe" was not used.

After five weeks of treatment, about 70 % of the subjects in all active treatment groups presented with either "none" or "slight". By contrast, the corresponding figure for the vehicle was below 53 %.

The changes during the course of the survey in the proportion of subjects rated in either of two combined score categories is depicted below.

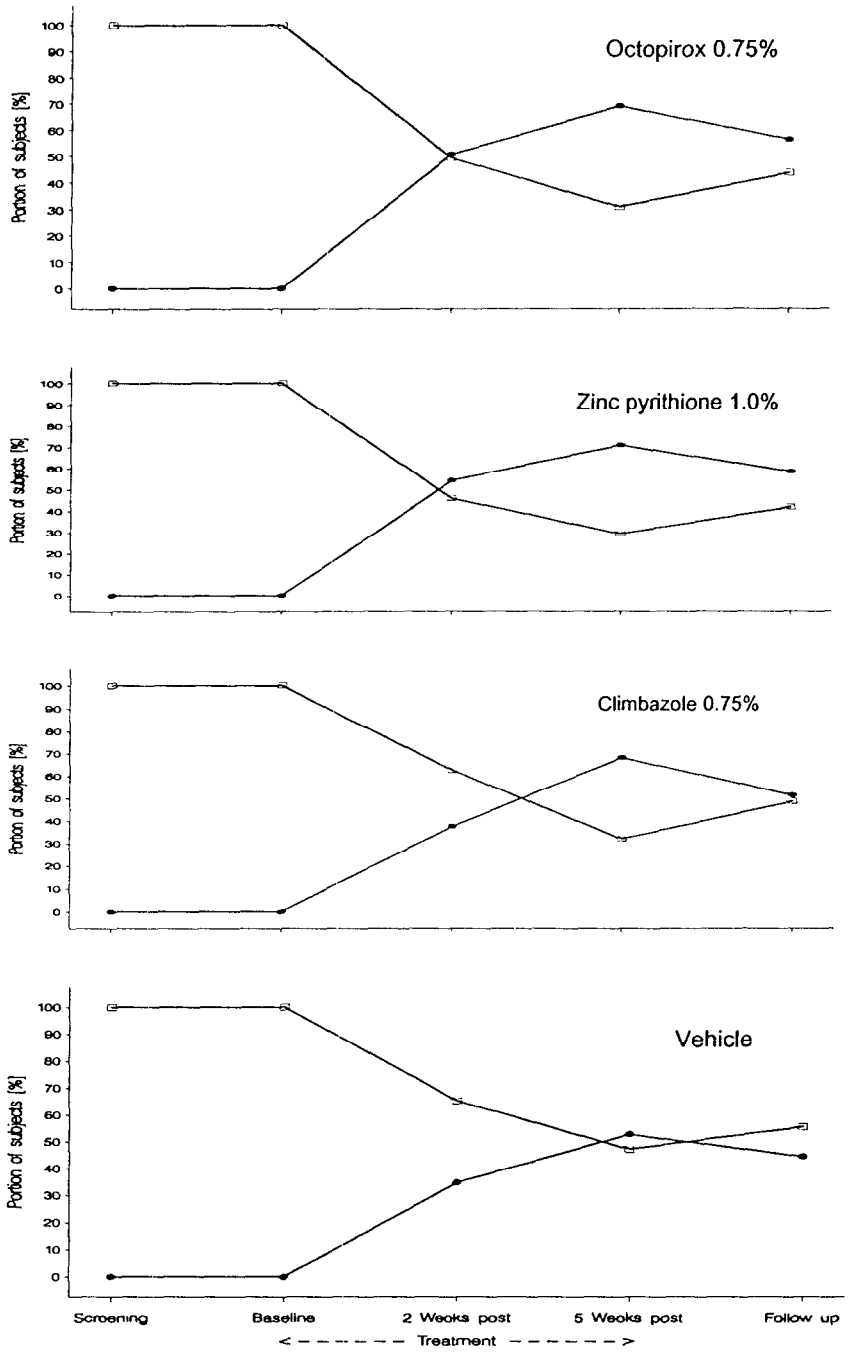


Figure 2
Scaling score - Combined categories during the course of the survey
Randomised treatment between baseline and 5 weeks post. ITT population (n=287)

●—●—●—●—● "none" and "slight"

□—□—□—□ "mild", "moderate" and "pronounced"

Upon the final assessment after 35 days of randomised treatment, a tendency towards improvement of scaling could be seen in all treatment groups. However, this improvement was clearly lowest in the vehicle group. In all three active treatment groups, more than two thirds of all subjects were scored as "none" or "slight" at the final assessment.

These findings as outlined above are substantiated by the results for pairwise treatment comparisons using the non-parametric Cochran-Mantel-Haenszel statistics:

Table 5
Scaling Score: Cochran-Mantel-Haenszel Test
Modified Ridit Scores, adjusted for centers
Alternative Hypothesis:
Mean scores differ at visit 4 (final assessment) ITT population (n=287)

			n	p-value
Octopirox 0.75%	*versus*	vehicle	143	0.0475
Zinc pyrithione 1%	*versus*	vehicle	144	0.0134
Climbazole 0.75%	*versus*	vehicle	144	0.0273
Octopirox 0.75%	*versus*	Zinc pyrithione 1%	143	0.3029
Octopirox 0.75%	*versus*	Climbazole 0.75%	143	0.8382

For all three active treatment groups the comparison of the scaling score against vehicle revealed a statistically significant p-value ($p < 5$ %).

By contrast, the comparisons of Octopirox with either of the other two active treatment groups did not result in a statistically significant difference. This however should not be interpreted as a statistical proof of equivalence, because the present survey and its hypotheses were not designed for analysis of equivalence.

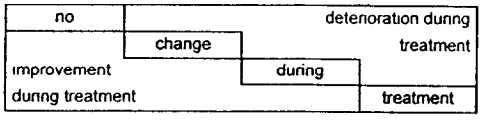
In all treatment groups a slight deterioration in the scaling score could be seen at the follow-up visit, after two weeks of treatment with shampoo base.

As a further measure of depicting the treatment results, the shifts in the scaling score from start to end of randomised treatment are presented below.

Table 6
Scaling score - Transition table
Figures denote percentage of subjects ITT population (n=287)

		Scaling score at final assessment after 5 weeks of treatment				
		none	slight	mild	moderate	pronounced
		Octopirox 0.75 % (n = 71)				
	none	-	-	-	-	-
	slight	-	-	-	-	-
	mild	2.8	25.4	9.9	4.2	-
	moderate	5.6	31.0	8.5	7.0	-
	pronounced	1.4	2.8	-	-	1.4
		Zinc pyrithione 1.0 % (n = 72)				
	none	-	-	-	-	-
	slight	-	-	-	-	-
Scaling	mild	5.6	26.4	5.6	2.8	-
score	moderate	13.9	23.6	9.7	5.6	-
	pronounced	1.4	-	1.4	4.2	-
		Climbazole 0.75 % (n = 72)				
at	none	-	-	-	-	-
	slight	-	-	-	-	-
baseline	mild	13.9	18.1	9.7	1.4	-
	moderate	2.8	31.9	9.7	6.9	-
	pronounced	-	1.4	1.4	2.8	-
		Vehicle (n = 72)				
	none	-	-	-	-	-
	slight	-	-	-	-	-
	mild	5.6	23.6	15.3	2.8	-
	moderate	2.8	18.1	9.7	16.7	1.4
	pronounced	-	2.8	-	-	1.4

Reading example:
31.0 % of the Octopirox subjects changed from „moderate" at baseline to „slight" at the final assessment.



The poorest result was observed for the vehicle group: Almost half of all subjects (47.9 %) remained unchanged or even deteriorated in the scaling score during the course of treatment.

In the Octopirox group more than two thirds (69.0 %) of the subjects improved to "none" or "slight" at the end of treatment. This was similar to the other two active groups.

This beneficial effect of Octopirox treatment was particularly marked for the severe cases of seborrhoeic dandruff: Of the four subjects, who were scored as "pronounced" at baseline only one (1.4 % of the total) remained unchanged during the course of the survey; the other three improved markedly to either "none" or "slight" at the end of treatment. By contrast, in the Zinc pyrithione group, among the five subjects presenting with "pronounced" at baseline, only one changed to "none"; the remaining four subjects still scored with "mild" (1 subject) or "moderate" (3 subjects) at the final assessment. The Climbazole group (four subjects with "pronounced" at baseline) showed a picture similar to the Zinc pyrithione group.

Size of scalp area affected

The percentage of the scalp area affected during the course of the survey is tabulated below.

Table 7
Percentage of affected scalp area
Figures denote percentage of subjects ITT population (n=287)

	0 - <10 %	10 - <20 %	20 - <30 %	30 - <50 %	50 - <75 %	75 - 100 %
			Octopirox 0.75%			
Screening	1.4	8.5	23.9	23.9	21.1	21.1
Baseline	**2.8**	**5.6**	**18.3**	**28.2**	**28.2**	**16.9**
Interim	15.5	26.8	25.4	19.7	8.5	4.2
Final	**32.4**	**31.0**	**18.3**	**9.9**	**5.6**	**2.8**
Follow up	33.8	25.4	5.6	21.1	11.3	2.8
			Zinc pyrithione 1.0%			
Screening	2.8	12.5	18.1	20.8	31.9	13.9
Baseline	**1.4**	**11.1**	**19.4**	**29.2**	**23.6**	**15.3**
Interim	18.1	20.8	25.0	22.2	9.7	4.2
Final	**29.2**	**38.9**	**11.1**	**11.1**	**9.7**	-
Follow up	38.9	19.4	15.3	18.1	8.3	-
			Climbazole 0.75%			
Screening	2.8	9 7	12.5	31.9	30.6	12.5
Baseline	**1.4**	**9.7**	**18.1**	**27.8**	**29.2**	**13.9**
Interim	9.7	25.0	16.7	27.8	13.9	6.9
Final	**36.1**	**19.4**	**18.1**	**15.3**	**9.7**	**1.4**
Follow up	30.6	26.4	18.1	16.7	8.3	-
			Vehicle			
Screening	2.8	9.7	15.3	23.6	31.9	16.7
Baseline	**2.8**	**8.3**	**16.7**	**23.6**	**34.7**	**13.9**
Interim	8.3	18.1	19.4	26.4	25.0	2.8
Final	**16.7**	**27.8**	**25.0**	**16.7**	**11.1**	**2.8**
Follow up	15.3	25.0	25.0	25.0	6.9	2.8

While the inclusion criteria did not specify the affected scalp area, the respective categories at baseline containing most subjects in all treatment groups were "30-50 %" and "50-75 %". It can be concluded that the baseline conditions with respect to affected scalp area were reasonably well matched across the treatment groups.

As for the scaling score, a tendency towards improvement of the size of the affected area during the course of treatment could be seen in all treatment groups: After 5 weeks of treatment there was a clear shift towards a reduction in the affected scalp area. This improvement was clearly lowest in the vehicle group, with only minor differences between the three active treatment groups.

Combination of "Scaling" and "Scalp area affected"

Since for the subjects affected by seborrhoeic dandruff of the scalp, both variables, "scaling score" and "percentage of affected scalp area" are of crucial importance, a synoptical examination was scheduled after unblinding.

A graphical synopsis for both parameters is depicted below.

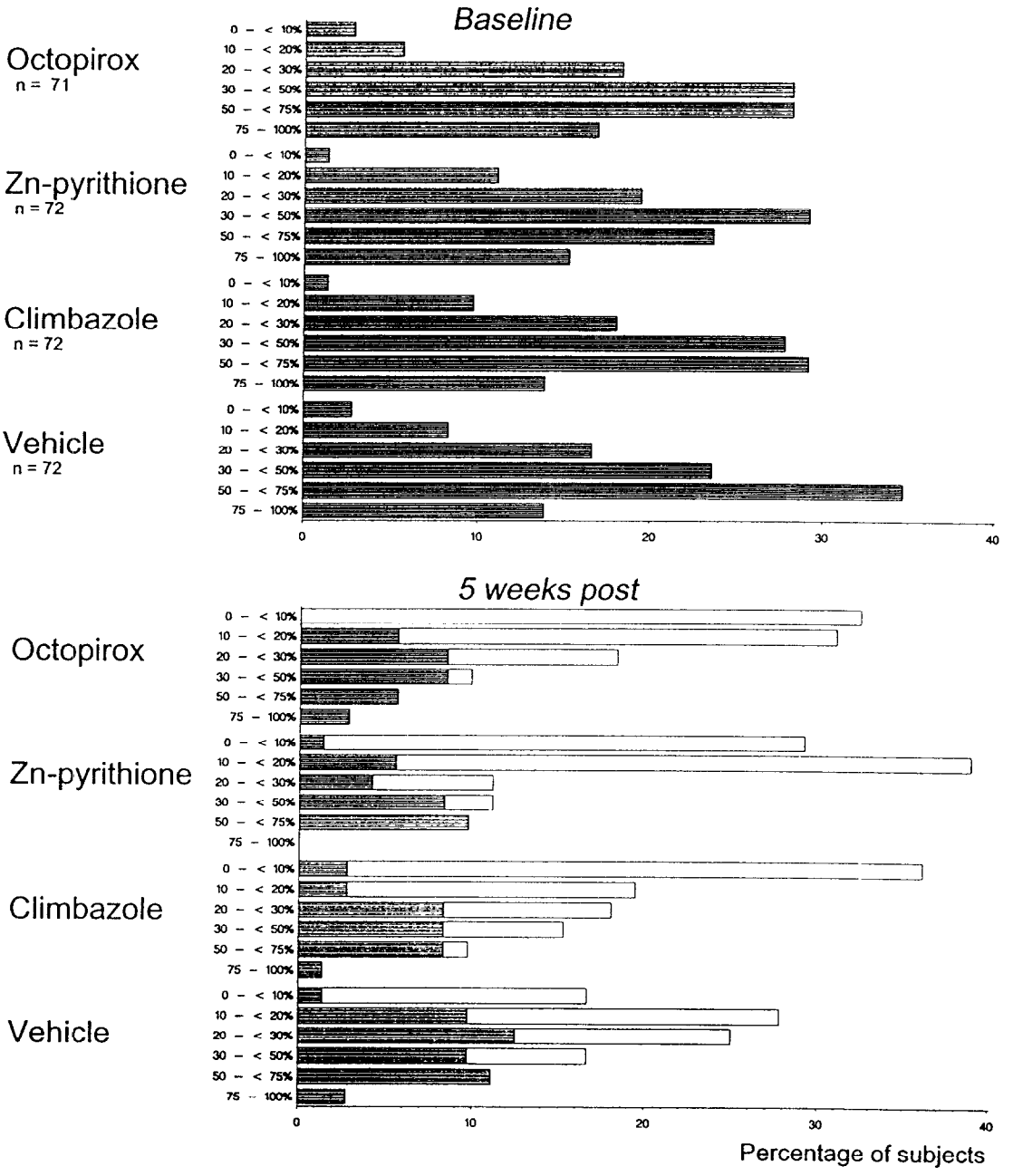


Figure 3
Scaling score and percentage of affected scalp area
Results for baseline (upper panel) and after 5 weeks of treatment (lower panel), ITT population. The ordinates depict for each treatment the six categories for "Percentage of affected scalp area". The corresponding ratings for the scaling score are summarised into two combined categories:

□ "none" and "slight"
■ "mild", "moderate" and "pronounced"

As governed by the selection criteria, no subjects with "none" or "slight" at baseline were included.

Reading example for Octopirox: After 5 weeks of treatment more than 30 % of the Octopirox subjects were rated with "10 to <20% scalp area affected"; the scaling score in most of these subjects was "none" or "slight".

As already pointed out above, the baseline conditions with respect to scaling score and affected scalp area were reasonably well matched across the treatment groups.

The results presented above separately for the two variables are visually supported in the above figure: In all treatment groups an improvement in both scaling score and percentage affected scalp area was recorded during the course of the survey. This improvement was lowest in the vehicle group, whereas little differences between the active treatment groups can be seen.

In addition to the synoptical presentation above, a combined score was formed by adding for each individual at each visit the respective outcomes for "scaling score" (0-5) and "percentage of affected scalp area" (0-5). The results for this sumscore 2 (0-10) are given below.

Table 8
Sumscore 2:
Combined score for "Scaling" and "Affected scalp area"
Figures denote means and SD ITT population (n=287)

Octopirox 0.75%	Screening	5.9	1.8
	Baseline	5.9	1.6
	Interim	3.6	1.9
	Final	2.7	2.1
	Follow up	3.2	2.5
Zinc pyrithione 1%	Screening	5.7	1.7
	Baseline	5.8	1.5
	Interim	3.6	2.0
	Final	2.5	2.0
	Follow up	2.8	2.2
Climbazole 0.75%	Screening	5.8	1.6
	Baseline	5.8	1.6
	Interim	4.2	2.0
	Final	2.7	2.1
	Follow up	3.0	2.1
Vehicle	Screening	5.8	1.6
	Baseline	5.8	1.6
	Interim	4.5	1.9
	Final	3.5	2.1
	Follow up	3.6	2 0

Again, while the baseline conditions were comparable across the treatment groups, a more pronounced improvement during the course of the survey could be seen in the

active treatment groups as compared with the vehicle group. This finding is reflected in the results of the corresponding Cochran-Mantel-Haenszel Test as given below.

Table 9
Sumscore 2: Cochran-Mantel-Haenszel Test
Modified Ridit Scores, adjusted for centers
Alternative Hypothesis:
Mean scores differ at visit 4 (final assessment) ITT population (n=287)

			n	p-value
Octopirox 0.75%	*versus*	vehicle	143	0.0120
Zinc pyrithione 1%	*versus*	vehicle	144	0.0041
Climbazole 0.75%	*versus*	vehicle	144	0.0608
Octopirox 0.75%	*versus*	Zinc pyrithione 1%	143	0.4626
Octopirox 0.75%	*versus*	Climbazole 0.75%	143	0.6586

For Octopirox and for Zinc pyrithione the comparison of the sumscore 2 against vehicle revealed a statistically significant p-value ($p < 5\ \%$). The corresponding value for Climbazole just failed to reach this level.

The comparisons of Octopirox with either of the other two active treatment groups did not result in a statistically significant difference. Again, this should not be interpreted as a statistical proof of equivalence, because the present survey and its hypotheses were not designed for analysis of equivalence.

Further efficacy evaluations

Sumscore 1

The sumscore 1 (the primary efficacy parameter according to the protocol) derived from the individual clinical symptoms of "scaling", "itching" and "inflammation". Results of the descriptive and test statistics for the ITT population are summarised below.

Table 10
Sumscore 1, median and p-values for CMH statistics
modified ridit scores, adjusted for centers

		Octopirox 0.75%	Zinc pyrithione 1.0%	Climbazole 0.75%	Vehicle
		ITT population			
median	Baseline	7.0	7.0	7.0	7.0
	5 weeks post	2.0	2.0	2.0	3.0
p-value	versus Vehicle	0.0830	0.0337	0 1731	-
	versus Octopirox	-	0.5872	0.9416	-
		VC population			
median	Baseline	7.0	7.0	7.0	7.0
	5 weeks post	2.0	2.0	2.0	3 0
p-value	versus Vehicle	0.0721	0.0724	0.2337	-
	versus Octopirox	-	0.7396	0.5609	-

In all treatment groups there was a clear tendency towards improvement of the sumscore. This held true for both the ITT and the VC population. The weakest improvement was recorded in the vehicle group, which changed in the ITT populations from a baseline median of 7.0 to a median of 3.0 at visit 4 after five weeks of treatment (vehicle mean values were 7.0 and 3.6 for baseline and visit 4 respectively).

According to the protocol the confirmatory part of these analyses is the comparison of Octopirox versus vehicle. For both analysis populations, the significance level of 0.05 was just missed. On a descriptive level the two remaining active treatments were also tested versus vehicle. The only p-value below 0.05 was reached for Zinc pyrithione in the ITT population (0.0337), which however was found to be above 0.05 for the corresponding VC population (0.7396). Again on a descriptive level Octopirox was compared to the two other active treatments. All comparisons in either analysis population revealed p-values above 0.5, which did not indicate that there are any significant differences. This however should not be interpreted as a statistical proof of equivalence, because the present survey and its hypotheses were not designed for analysis of equivalence.

Itching score

The percentages of subjects recorded for each assessment category of the itching score at each survey visit are presented in the table below.

Table 11
Itching score
Figures denote percentage of subjects ITT population (n=287)

	none	slight	mild	moderate	pronounced	severe
			Octopirox 0.75%			
Screening	7.0	9.9	31.0	40.8	9.9	1.4
Baseline	9.9	25.4	33.8	19.7	9.9	1.4
Interim	32.4	38.0	15.5	8.5	5.6	-
Final	35.2	42.3	14.1	5.6	2.8	-
Follow up	36.6	29.6	14.1	15.5	4.2	-
			Zinc pyrithione 1.0%			
Screening	2.8	9.7	38.9	38.9	9.7	-
Baseline	4.2	8.3	41.7	34.7	9.7	1.4
Interim	26.4	41.7	18.1	8.3	5.6	-
Final	43.1	37.5	11.1	6.9	1.4	-
Follow up	44.4	23.6	15.3	13.9	2.8	-
			Climbazole 0.75%			
Screening	5.6	11.1	38.9	36.1	8.3	-
Baseline	2.8	12.5	36.1	34.7	12.5	1.4
Interim	9.7	55 6	16.7	8.3	9.7	-
Final	30.6	48.6	13.9	4.2	2.8	-
Follow up	23.6	38.9	20.8	11.1	5.6	-
			Vehicle			
Screening	2.8	11.1	27.8	47.2	11.1	-
Baseline	5.6	19.4	33.3	30.6	8.3	2.8
Interim	19.4	43.1	18.1	11.1	5.6	2.8
Final	29.2	41.7	18.1	5 6	4.2	1.4
Follow up	23.6	40.3	19.4	13 9	2.8	-

Apart from there being slightly more cases treated with Octopirox with no or slight itching, the treatment groups were well matched during baseline. During treatment there was a tendency towards improvement of itching in all treatment groups. After 35 days (by visit 4) of randomised treatment the percentage of subjects categorised as 'none' for itching was highest in the Zinc pyrithione 1% group (43.1%) and lowest in the vehicle group (29.2%). The proportion of subjects with a score of 'severe' was similar between the treatments although there was a small excess in the vehicle group during visits 2, 3 and 4.

Inflammation score

The percentages of subjects recorded for each assessment category of the inflammation score at each survey visit are presented in the table below.

Table 12
Inflammation score
Figures denote percentage of subjects ITT population (n=287)

	none	slight	mild	moderate	pronounced	severe
			Octopirox 0.75%			
Screening	-	-	71.8	22.5	5.6	-
Baseline	-	-	73.2	26.8	-	-
Interim	35.2	33.8	26.8	4.2	-	-
Final	57.7	25.4	9.9	7.0	-	-
Follow up	49.3	31.0	12.7	7.0	-	-
			Zinc pyrithione 1.0%			
Screening	-	-	73 6	23.6	2.8	-
Baseline	-	-	75.0	25.0	-	-
Interim	30.6	38.9	25.0	5.6	-	-
Final	52.8	27.8	16.7	2 8	-	-
Follow up	54.2	23.6	18.1	4.2	-	-
			Climbazole 0.75%			
Screening	-	-	86.1	12.5	1.4	-
Baseline	-	-	81.9	18.1	-	-
Interim	31.9	31.9	27.8	6.9	1.4	-
Final	61.1	22.2	11.1	5.6	-	-
Follow up	56.9	23.6	11.1	8.3	-	-
			Vehicle			
Screening	-	-	70.8	29.2	-	-
Baseline	-	-	79.2	20.8	-	-
Interim	22.2	38.9	29.2	9.7	-	-
Final	44.4	37.5	12.5	4.2	1.4	-
Follow up	48.6	31.9	18.1	1.4	-	-

The treatments were well matched during baseline and during treatment there was a tendency towards improvement of inflammation in all treatment groups. After 35 days (by visit 4) of randomised treatment the percentage of subjects categorised as 'none' or 'slight' was similar for the Octopirox 0.75% (83.1%), Zinc pyrithione 1% (80.6%), Climbazole 0.75% (83.3%) and vehicle (81.9%) groups.

Additional description

A summary of the results of the additional description of the disease (with regards to presence or absence of moistening, pustules or scratch marks) for percentages of subjects in the ITT group are summarised below.

Table 13
Additional description of the disease
Figures denote percentages of subjects ITT population (n=287)

		MOISTENING (%)		PUSTULES (%)		SCRATCH MARKS (%)		Total
		absent	present	absent	present	absent	present	N=100%
Treatment	visit							
Octopirox 0.75%	visit 1	88.7	11.3	93.0	7.0	77.5	22.5	71
	visit 2	85.9	14.1	91.5	8.5	83.1	16.9	71
	visit 3	93.0	7.0	95.8	4.2	94.4	5.6	71
	visit 4	94.4	5.6	93.0	7.0	97.2	2.8	71
	visit 5	94.4	5.6	94.4	5.6	94.4	5.6	71
Zinc pyrithione 1%	visit 1	87.5	12.5	91.7	8.3	79.2	20.8	72
	visit 2	87.5	12.5	90.3	9.7	80.6	19.4	72
	visit 3	95.8	4.2	94.4	5.6	94.4	5.6	72
	visit 4	95.8	4.2	98.6	1.4	95.8	4.2	72
	visit 5	97.2	2.8	98.6	1.4	97.2	2.8	72
Climbazole 0.75%	visit 1	88.9	11.1	95.8	4.2	83.3	16.7	72
	visit 2	90.3	9.7	93.1	6.9	87.5	12.5	72
	visit 3	91.7	8.3	94.4	5.6	91.7	8.3	72
	visit 4	93.1	6.9	95.8	4.2	94.4	5.6	72
	visit 5	97.2	2.8	95.8	4.2	93.1	6.9	72
Vehicle	visit 1	88.9	11.1	91.7	8.3	76.4	23.6	72
	visit 2	88.9	11.1	95.8	4.2	87.5	12.5	72
	visit 3	93.1	6.9	97.2	2.8	97.2	2.8	72
	visit 4	95.8	4.2	97.2	2.8	95.8	4.2	72
	visit 5	95.8	4.2	97.2	2.8	100.0		72

For all treatment groups there was a trend towards improvement during the course of randomised treatment. By visit 4, there were only minor differences between the treatment groups.

Additional hair characteristics

Results at visits 3 and 4 for additional hair characteristics (wet combing/brushing; dry combing/brushing; greasy) show that the additional hair characteristics were rated as being unchanged or better with a minority in all randomised treatment groups being rated as worse.

Diagnosis of recurrence of seborrhoeic dandruff of the scalp at visit 5

Results of the final examination visit (i.e. visit 5 on day 70 : follow-up visit 14 days after the end of the 5 week treatment period) for the diagnosis of the recurrence (none, slight, mild, moderate, pronounced) of seborrhoeic dandruff of the scalp (number and percentage) for both the ITT population are presented below.

Table 14
Diagnosis of recurrence of seborrhoic dandruff at visit 5
Figures denote number and percentages of subjects ITT population (n=287)

		N	%
treatment	diagnosis		
Octopirox 0.75%	none	14	20
	slight	28	39
	mild	10	14
	moderate	16	23
	pronounced	3	4
Zinc pyrithione 1%	none	21	29
	slight	24	33
	mild	13	18
	moderate	13	18
	pronounced	1	1
Climbazole 0.75%	none	18	25
	slight	21	29
	mild	21	29
	moderate	11	15
	pronounced	1	1
Vehicle	none	18	25
	slight	20	28
	mild	15	21
	moderate	17	24
	pronounced	2	3

During the follow-up period, improvements against seborrhoeic dandruff observed during treatment tended to be reversed in most subjects, regardless of which treatment they had received during the treatment period. The proportion experiencing slight, mild, moderate or pronounced effect was similar across the treatment groups.

8. SUMMARY AND CONCLUSIONS

The results of this double blind vehicle controlled survey clearly demonstrated the beneficial effect of twice weekly application of Octopirox 0.75 % in the treatment of seborrhoeic dandruff. This held true for both, the improvement of the scaling score as well as the proportion of the affected scalp area.

While - in accordance with the inclusion criteria - all subject had at baseline a scaling score of "mild" or worse, more than two thirds (69.0 %) of the subjects treated with Octopirox 0.75 % scored either "none" or "mild" at the end of the five week treatment period. The corresponding results for the other active treatment groups were 70.8 % (Zinc pyrithione 1%) and 68.1 % (Climbazole 0.75 %). This contrasts to the vehicle group which exhibited the weakest improvement among all treatment groups (52.8 %).

Applying non-parametric statistics, the difference in scaling score results between Octopirox 0.75 % and vehicle proved to be significant. Similar signifance was found for the other active treatment groups when compared with vehicle. In the line of this, the comparison of Octopirox 0.75 % with the active comparators Zinc pyrithione 1.0% and Climbazole 0.75% did not reveal significant differences.

Similarily favourable results were found for the sumscore 2, which combines the outcome for both scaling and proportion of affected scalp area. The difference in this parameter between Octopirox 0.75 % and vehicle proved to be statistically significant, with a similar signifance found for Zinc pyrithione 1%, while Climbazole 0.75 % just failed to reach the level of significance.

There was no formal collection of safety data (adverse events, serious adverse events, laboratory data, local tolerance) during this survey and so no conclusions concerning safety or tolerability can be reached.

It can be concluded that Octopirox 0.75 % is effective in the treatment of seborrhoeic dandruff in Asian people under tropical conditions.

9. REFERENCES

Farr P.M. & Shuster S. 1984
Treatment of seborrhoeic dermatitis with topical ketoconazole.
Lancet 2: 1271-1272

Ford G.P., Farr P.M. & Shuster S. 1984
The response of seborrhoeic dermatitis to ketoconazole.
Br. J. Derm. 111: 603-607

Hewin 1994
The role of chemical specialities used in personal care products in Western Europe, North America and Japan.
Hewin International Inc., Van Leyenberghlaan 159, Amsterdam NL

Lehmann E.L. & D'Abrea H.J.M. 1975
Nonparametrics. Statistical methods based on ranks.
Holden-Day - San Francisco

Rivolta S. 1873
Parasiti vegetali.
Guilio Speirani - Torino 1st ed. pp 469-471

Shuster S. 1984
The aetiology of dandruff and the mode of action of therapeutic agents.
Br. J. Derm. 111: 235-242

LIST OF APPENDICES